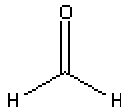


Formaldehyde
CAS Registry Number 50-00-0



I. Physical and Chemical Properties

<i>Description</i>	Colorless irritant gas
<i>Molecular formula</i>	CH ₂ O
<i>Molecular weight</i>	30.03
<i>Air concentration conversion</i>	1 ppb = 1.23 µg/m ³

II. Overview

Human studies suggest that children are more sensitive than adults to formaldehyde toxicity. In a study examining effects in both children and adults, Krzyzanowski *et al.* (1990) reported that increasing formaldehyde levels appeared to be associated with greater impacts on lung function in children than in adults in the same household. Krzyzanowski *et al.* (1990) found that formaldehyde in the home affects lung function in children at concentrations as low as 30 ppb, especially in asthmatics, as measured by peak expiratory flow rate. Adults in the same homes appeared to be less affected. This study also found that in homes with greater formaldehyde exposures (between 60 and 120 ppb), there was a greater prevalence of diagnosed asthma and chronic bronchitis in children, but not adults.

While Krzyzanowski *et al.* (1990) is the only study that directly compares the effects of formaldehyde in adults and children, there are several other studies that indicate that children are more sensitive to formaldehyde toxicity than adults. Of the numerous studies in adults (primarily occupational studies) the NOAEL and LOAEL are 32 µg/m³ (26 ppb) and 92 µg/m³ (75 ppb), respectively, after adjustment for exposure continuity. (These data are based on nasal and eye irritation observed in Wilhelmsson and Holstrom (1992), and histological lesions in the nasal cavity documented in Edling *et al.* (1988), and form the basis of the chronic REL, described in detail in OEHHA (2000)). However, studies in children, including the Krzyzanowski study above, indicate adverse health impacts in children at concentrations as low as 30 ppb. Wantke *et al.* (1996) reported that formaldehyde-specific IgE and respiratory symptoms were reduced when children transferred from schools with formaldehyde concentrations of 43 to 75 ppb to schools with concentrations of 23 to 29 ppb. Garrett *et al.* (1999) reported increased sensitization associated with the formaldehyde level in children's homes which had a median value of 15.8 µg/m³ (12.6 ppb). And Franklin *et al.* (2000) reported significantly higher

exhaled nitric oxide, an indicator of airway inflammation, in the breath of children living in homes with formaldehyde concentrations greater than 50 ppb than in the breath of those children living in homes with formaldehyde levels below 50 ppb. These human studies are not entirely consistent with each other, and there is potential for confounding in each. Nevertheless, taken together, they suggest that children may be more sensitive to formaldehyde toxicity than adults.

As described in Section II of the Introduction, OEHHA considers asthma to impact children more than adults and thus substances that either exacerbate or induce asthma should be considered for listing under SB 25. While chamber studies in adults have not been convincing that formaldehyde exposure exacerbates asthma, the studies in adults may not be applicable to allergic asthma in children. As previously noted, Krzyzanowski *et al.* (1990) found that asthmatic children were more affected by formaldehyde than non-asthmatic children. In addition, allergic sensitization, as measured by elevated levels of formaldehyde-specific IgE, has been noted in two studies of children exposed to environmental levels of formaldehyde (Wantke *et al.*, 1996; Garrett *et al.*, 1999). The allergic sensitization may make children more sensitive to development of serious conditions such as asthma, although this has not been studied for formaldehyde. In addition to the data in children, animal data provide support for the contention that formaldehyde exposure may exacerbate asthma. Amdur (1960) showed that formaldehyde has a marked effect on airway resistance and compliance in guinea pigs. More importantly, Swieczkowski *et al.* (1993) showed that duration of exposure is important to the induction of airway hyperreactivity from formaldehyde. In this latter study, an 8-hour exposure to 1 ppm formaldehyde produced greater than expected effects on airway constriction compared to a 2-hour exposure at higher concentrations, suggesting that prolonged, low-level formaldehyde exposures may generate abnormal physiologic responses in the airways not detectable after acute exposures.

In addition to the human and animal studies of formaldehyde toxicity, OEHHA also considered exposure. Typical urban ambient air levels and indoor air levels can exceed the chronic REL of 2 ppb. Moreover, children are frequently exposed to levels of formaldehyde exceeding the chronic REL in indoor air of classrooms. A compilation of monitored California classrooms showed that children were exposed to a mean of 21 ppb and a maximum of 98 ppb (CARB, 2001, interdepartmental transmission). For these reasons, formaldehyde is considered a priority chemical for evaluation of potential differential effects on infants and children.

III. Principal Sources of Exposure

A. Ambient Air

Formaldehyde is released to outdoor air from both natural and industrial sources. Formaldehyde is formed naturally in the atmosphere during the oxidation of hydrocarbons, which react with hydroxyl radicals and ozone to form formaldehyde and other aldehydes. Outdoor air concentrations in urban environments ranged from 1-20 $\mu\text{g}/\text{m}^3$ and depend on local conditions (WHO, 1989; IARC, 1995). In 1998 and 1999 in California, the ambient mean formaldehyde concentration was 3.6 $\mu\text{g}/\text{m}^3$ (2.9 ppb) with a maximum of 14.3 $\mu\text{g}/\text{m}^3$ (11.5 ppb) (see Table 1 below). A major source of formaldehyde in urban air is incomplete combustion of hydrocarbon fuels, especially from vehicle emissions. Urban air

concentrations in heavy traffic or during severe inversions can range up to $100 \mu\text{g}/\text{m}^3$ (WHO, 1989). Gaffney *et al.* (1997) found that in urban areas the introduction of oxygenated fuels led to increased anthropogenic emissions of formaldehyde during the winter, the season these fuels are used. Formaldehyde in vehicle emissions in 1994 were found to increase by 13% within 2 months after the average oxygen content of fuels sold in the San Francisco Bay area increased from 0.3 to 2.0% by weight (Kirchstetter *et al.*, 1996). In the Los Angeles area, the contribution of photochemical production of formaldehyde to levels in the air predominates over direct vehicular emissions (Grosjean and Wright, 1983). Numerous manufacturing processes also contribute to formaldehyde levels in the atmosphere (see below).

B. Indoor air

The emission of formaldehyde from common household products can be very high. In chamber studies simulating typical home conditions (70°F, 50% RH, 1.0 air exchange per hour) bare urea-formaldehyde wood products (particleboard, and plywood; product loading $0.46 \text{ m}^2/\text{m}^3$) have emission rates from a high of 1580 to a low of $9 \mu\text{g}/\text{m}^2/\text{hr}$ (CARB, 1996). Wet products like latex paints, wallpaper, fingernail hardener, nail polish, and commercially applied floor finish also emit formaldehyde. Commercially applied floor finish and fingernail hardener has very high initial rate of formaldehyde emission. Other indoor sources such as wood and gas stoves, kerosene heaters, and cigarettes contribute intermittently to indoor formaldehyde levels. In general, indoor environments consistently have higher concentrations than outdoor environments, because many building materials, consumer products, and fabrics emit formaldehyde (Cal/EPA, 1992).

A recent survey measured formaldehyde concentrations inside conventional California residences. The mean value was $11 \mu\text{g}/\text{m}^3$ (9 ppb) and the maximum was $39 \mu\text{g}/\text{m}^3$ (31 ppb) (Avol, 1996; footnote "a" in Table 1). Current manufactured home concentrations are estimated to be 49 percent of the 1984-85 California Department of Health Services' (DHS) manufactured home study results. This reduction is based on the reduction of formaldehyde emissions from building materials that has occurred since the DHS manufactured home study was conducted (see footnote "b" in Table 1). The resulting mean concentration is $45 \mu\text{g}/\text{m}^3$ (36 ppb) and the maximum is $282 \mu\text{g}/\text{m}^3$ (227 ppb). A U.S. EPA study reported concentrations in public and commercial buildings. The mean value was $16 \mu\text{g}/\text{m}^3$ (13 ppb) and the maximum was $32 \mu\text{g}/\text{m}^3$ (26 ppb). Measurements inside schools have obtained a considerable range of formaldehyde concentrations. In 104 classrooms monitored in California, the mean concentration was $26 \mu\text{g}/\text{m}^3$ (21 ppb) and the maximum was $122 \mu\text{g}/\text{m}^3$ (98 ppb) (see Table 1).

TABLE 1. Formaldehyde Concentrations for Various Locations

Location	Mean µg/m³ (ppb)	Max µg/m³ (ppb)	Source for Values
Conventional homes	11.3 (9.1)	38.8 (31.3)	USC study, 99 Southern California homes ^a
Manufactured homes	45 (36.3)	282 (227)	Approx. 600 mobile homes from study conducted by DHS in 1984 & 1985. The average of summer and winter values was reduced 49% of '84 and '85 levels. Based on known reductions in building material emissions. ^b
Public & Commercial Buildings	16 (12.9)	32 (25.8)	EPA BASE Study, 100 buildings. ^c Used office building concentration data for Offices and Public Buildings, Restaurants & Lounges, and Other Indoor Spaces.
Industrial Plant	16 (12.9)	32 (25.8)	Used Office building data concentration (no data for Industrial Plant)
School	26.2 (21.1)	121.5 (98.0)	Data from several schools, 104 classrooms monitored by ARB. Includes northern and southern California.
In-Vehicle (Sacramento)	9.3 (7.5)	18.5 (14.9)	ARB, estimated average of Sacramento runs ^d
In-Vehicle (Los Angeles)	15.3 (12.3)	23.6 (19.0)	ARB, estimated average of LA runs ^d
Outdoor	3.6 (2.9)	14.3 (11.5)	ARB, average of 1998 and 1999 statewide ambient means and maxima.

Conversion factor: 1 ppb = 1.24 µg/m³ @ 25 °C

- a Avol, E. (1996), "Residential Microenvironmental and Personal Sampling Project for Exposure Classification", draft final report to ARB, contract no. 92-317.
- b Emission rates from Pickrell and Kelly were compared. Particleboard emissions are 92% of what they were in 1983, interior plywood emissions are 15% of emissions in 1983, and paneling emissions are 39% of 1983 emissions. If one takes a straight average of these reductions in emissions, building emissions today are estimated to be 49% lower than emissions in the early 1980's.

Pickrell, J., et al (1983), " Formaldehyde Release Rate Coefficients from Selected Consumer Products", Environmental Science and Technology 17(12): 753-757.

Kelly, T., et al (1999), "Emission Rates of Formaldehyde from Materials and Consumer Products Found in California Homes", Environmental Science and Technology 33 (1): 81-88.
- c More information on the US EPA Building Assessment Survey and Evaluation (BASE) Study can be found at <http://www.epa.gov/iaq/base/index.html>.

- d Rodes, C., et al (1998), "Measuring Concentrations of Selected Air Pollutants Inside California Vehicles", final report to ARB, contract no. 95-339.

In-vehicle studies have found formaldehyde concentrations to be similar to concentrations measured outdoors. A southern California study found an average in-vehicle formaldehyde concentration of 15.3 $\mu\text{g}/\text{m}^3$ (12.5 ppb) and a maximum concentration of 35.3 $\mu\text{g}/\text{m}^3$ (28.8 ppb) during the summer of 1987 and winter of 1988 (Shikiya *et al.*, 1989). A study in Boston, Massachusetts, measured a mean formaldehyde concentration of 5.1 $\mu\text{g}/\text{m}^3$ (4.2 ppb) and a maximum concentration of 19.7 $\mu\text{g}/\text{m}^3$ (16.1 ppb) (Chan *et al.*, 1991a,b). A recent California study by Rodes *et al.* (1989; footnote "d" in Table 1) found concentrations in vehicles to be higher in Los Angeles and lower in Sacramento than found in the 1989 California study.

C. Emissions

Formaldehyde is released into the atmosphere from various manufacturing processes including: formaldehyde and resin manufacturing plants, plywood and particle-board mills, furniture factories and other wood product plants, paper and textile mills, garment factories, foundries, man-made mineral fiber plants, plastic production, and other miscellaneous processes such as photographic film manufacturing and development, embalming in funeral homes, and disinfecting in hospitals (IARC, 1995). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1,589,810 pounds of formaldehyde (CARB, 1999a). In 1997, the population-weighted annual average exposure in the South Coast Air Basin was estimated to be 4.7 ppb formaldehyde (CARB, 1999b). The statewide ambient air concentration for 1999 was calculated by ARB to be 3.2 ppb (4.0 $\mu\text{g}/\text{m}^3$).

IV. Potential for Differential Effects

A. Summary of Key Human Studies

One study was found in the literature that directly compares the effects of formaldehyde in adults and children (Krzyzanowski *et al.* (1990). Results of this study show that children are more sensitive than adults to formaldehyde toxicity. In addition, three other studies found respiratory effects in children at concentrations lower than generally found in adults (Wantke *et al.*, 1996; Garrett *et al.*, 1999; Franklin *et al.*, 2000). These four studies are summarized here. While they are not entirely consistent with each other and there is potential for confounding in each, nevertheless taken together they suggest that children may be more sensitive to formaldehyde toxicity than adults.

Krzyzanowski *et al.* (1990) studied the relationship of formaldehyde to chronic respiratory symptoms and pulmonary function in children and adults. The sample consisted of 298 children (5-15 years of age) and 613 adults in 202 households in Tuscon, Arizona. Formaldehyde measurements were made with passive samplers in homes during two 1-week periods. The investigation also obtained data on tobacco usage and nitrogen dioxide levels in the home, as well as parents' education and ethnicity. Data on chronic cough, chronic phlegm, wheeze, attacks of breathlessness, and doctor diagnoses of chronic bronchitis and of asthma were collected from self-completed questionnaires. Peak expiratory flow rates

(PEFR) were obtained during the evenings and mornings for up to 14 consecutive days for each individual. The average formaldehyde concentration was 26 ppb. In a few cases the concentration exceeded 90 ppb, with a maximum value of 140 ppb.

The analyses of the symptoms and diagnosed disease used three exposure groups, <40 ppb, 40-60 ppb, >60 ppb. Log-linear analyses controlled for possible confounding by current smoking, environmental tobacco smoke (ETS) in nonsmokers or children, economic status using educational level of adults, and ethnicity. In children but not adults, the study found significantly greater prevalence rates of asthma and chronic bronchitis in homes with formaldehyde levels of 60-120 ppb than in those less exposed, especially using kitchen levels. The trend was highly significant for chronic bronchitis ($p<0.001$) and significant for asthma ($p<0.03$). The trend disappeared with the exclusion of children also exposed to environmental tobacco smoke. The prevalence rates of chronic respiratory symptoms were not related to formaldehyde exposures in either children or adults.

A longitudinal random-effects analysis of PEFR used constant covariates, asthma status, tobacco status, and socioeconomic status. Time-dependent covariates were episodes of acute respiratory illness, time of day and nitrogen dioxide levels. In children, levels of PEFR decreased linearly with formaldehyde exposure. Exposure to 60 ppb formaldehyde reduced PEFR 22% relative to unexposed children. Similarly, exposure to 30 ppb formaldehyde decreased PEFR 10% relative to unexposed children. The effects in asthmatic children exposed to formaldehyde below 50 ppb were greater than in healthy ones. The effects in adults were less evident: decrements in PEFR due to formaldehyde over 40 ppb were seen only in the morning, and mainly in smokers. These regressions are controlled for the possible effect of confounders.

These results suggest that formaldehyde has a greater effect on several measures of respiratory health in children than in adults. It is noteworthy that statistically significant results were obtained in children but not adults, even though the number of adults was greater than that of children, thus increasing the statistical power to detect an effect. However, the paper does not report any direct statistical analysis to test for a difference. In children the effects on PEFR appear to occur at least as low as 26 ppb, which was the mean value for the study.

Wantke *et al.* (1996) evaluated whether IgE-mediated sensitization and symptoms in children were associated with formaldehyde exposure at school. They studied 62 8-year olds attending primary school in Vienna. None of the children had asthma or wheezy bronchitis. Indoor formaldehyde concentrations were measured in classrooms of two buildings, one frame construction with particleboard used extensively as paneling and the other a brick building. A radioallergosorbent test (RAST) was used to assess the specific IgE to formaldehyde in all children while attending the paneled classrooms and 3 months after transfer to the brick building. In all children symptoms were evaluated by questionnaire before and 3 months after changing classrooms.

Elevated formaldehyde-specific IgE were detected in children whose classroom formaldehyde levels ranged from 43 to 75 ppb. Two of the three children with pathologically high RAST readings (>2.0) were in classrooms with 75 ppb formaldehyde. An additional 21 children had elevated RAST readings

(1.3-1.9). Symptoms found in the affected children were headache, nose bleeding, rhinitis, fatigue, cough, dry nasal mucosa and burning eyes. There was a good correlation between symptoms and the formaldehyde concentrations in the classrooms. However, elevated IgE levels to formaldehyde did not correlate with symptoms. After transferring to the brick building (formaldehyde ranged from 23 to 29 ppb) IgE levels in 20 children with elevated values dropped significantly ($p<0.002$). Symptoms also declined significantly: headache ($p<0.02$), nose bleeding ($p<0.001$), rhinitis ($p<0.01$), fatigue ($p<0.01$), cough ($p<0.10$), dry nasal mucosa ($p<0.05$) but not burning eyes.

These results appear to show a remarkable drop in symptoms after the move to a different building. The reduction in formaldehyde-specific RAST suggests that at least a part of the drop in symptoms after only 3 months may have been influenced by the decline of formaldehyde concentration of 36 ppb on average, from 63 ppb to 26 ppb. However, potential confounders, such as seasonal effect from December to March, were not ruled out. These concentrations of formaldehyde are only for the school week; effective continuous equivalent concentrations would be lower.

Garrett *et al.* (1999) investigated the relationship of formaldehyde to chronic respiratory symptoms and allergic response to aeroallergens in children. A total of 148 children 7-14 years of age were included in the study, of whom 53 were asthmatic, distributed among 43 homes. Formaldehyde levels were measured with passive samplers on four occasions over the course of a year in 80 homes in the Latrobe Valley, Victoria, Australia. At the last visit a respiratory questionnaire was completed for eight symptoms: cough, cough in the morning, shortness of breath, waking due to shortness of breath, wheeze/whistling, asthma attacks, chest tightness, and chest tightness in the morning. During the middle of the year, skin prick tests were performed with 12 environmental allergens, including four applications of fungi.

The median indoor formaldehyde level was $15.8 \mu\text{g}/\text{m}^3$ (12.6 ppb), with a maximum of $139 \mu\text{g}/\text{m}^3$ (111 ppb). The mean outdoor level was $0.7 \mu\text{g}/\text{m}^3$, with a range of 0.3 to $15.3 \mu\text{g}/\text{m}^3$. There was no significant association between formaldehyde and other contaminants.

There was an association between formaldehyde exposure and atopy in children. Parental asthma and parental allergy were found to be associated with current formaldehyde; so the children's association of atopy and formaldehyde was confirmed in those homes with parents having no asthma history. A logistic regression including an adjustment for gender and parental asthma found an odds ratio for atopy of 1.40 (0.98-2.00, 95% CI) associated with an increase in bedroom formaldehyde levels of $10 \mu\text{g}/\text{m}^3$. There was a similar odds ratio for an increase of $20 \mu\text{g}/\text{m}^3$ at the highest recorded level in the home. Furthermore, more severe allergic sensitization was demonstrated with increasing formaldehyde exposure. Also there was a marked jump in positive skin prick tests for the $20\text{-}50 \mu\text{g}/\text{m}^3$ (16- 41 ppb) and the over- $50 \mu\text{g}/\text{m}^3$ groups in comparison to the less-than- $20 \mu\text{g}/\text{m}^3$ group, all these concentrations representing the highest recorded level in the home. The authors reported that there was no significant increase in the adjusted odds ratio of asthma or respiratory symptoms with formaldehyde exposure. However, among children suffering from respiratory symptoms, higher symptom scores were noted in those exposed to higher formaldehyde levels after adjustment for parental asthma status. There also

was a marked jump in respiratory symptom scores for the 20-50 $\mu\text{g}/\text{m}^3$ and over 50 $\mu\text{g}/\text{m}^3$ groups in comparison to the less than 20 $\mu\text{g}/\text{m}^3$ group, all at the highest recorded level in the home.

These results suggest that low-level exposure to indoor formaldehyde may increase the risk of allergic sensitization to common aeroallergens in children. The lack of a positive adjusted risk for asthma prevents the positive adjusted risk for atopy from being linked to respiratory disease in this study.

In children the effect of formaldehyde on atopy appears to rise abruptly between the lowest and the middle exposure groups, suggesting an effect occurring no higher than the range of 16 to 41 $\mu\text{g}/\text{m}^3$ which represented the highest recorded formaldehyde levels in the home. This jump is consistent with the 34% rise in atopy for an increase of 16 $\mu\text{g}/\text{m}^3$ in the highest recorded formaldehyde level.

TABLE 2. Distribution of atopic and nonatopic children by highest formaldehyde exposure

Formaldehyde exposure group	N	Nonatopic N=57	Atopic N=88	Proportion atopic
<20 $\mu\text{g}/\text{m}^3$	30	20	10	0.33
20-50 $\mu\text{g}/\text{m}^3$	75	27	48	0.64
>50 $\mu\text{g}/\text{m}^3$	40	10	30	0.75

Linear trend $p < 0.001$

Source: Garrett *et al.* (1999)

Franklin *et al.* (2000) investigated possible inflammatory effects of formaldehyde at levels typically found in the home. The study recruited 224 healthy children 6 to 13 years of age (116 girls). Formaldehyde in homes was monitored using a passive sampling technique. As an indicator of respiratory inflammation, exhaled nitric oxide was measured directly into a fast response chemiluminescence nitric oxide analyzer. Lung function (spirometry) tests and skin prick tests for seven common allergens were conducted on the children. Housing factors were obtained from a questionnaire. The exhaled nitric oxide data and the spirometric data were each analyzed by multilinear regression after including housing factors found to be of marginal relationship in a bivariate screening analysis. The model also included the child's age and atopic status, because of a previously established relationship.

The formaldehyde levels measured in homes were found not to be related to either spirometric outcome, forced vital capacity or forced expiratory volume in one minute. However, exhaled nitric oxide levels were significantly elevated in children living in homes with average formaldehyde levels ≥ 50 ppb ($p=0.02$). Exhaled nitric oxide levels (geometric mean) were 15.5 ppb (95% CI: 10.5 to 22.9 ppb) for children from homes with formaldehyde concentrations ≥ 50 ppb compared with 8.7 ppb (7.9 to 9.6)

for children from homes with formaldehyde concentrations < 50 ppb. After using a multiple regression to control for other variables, the result became highly significant ($p=0.002$).

In view of apparent precautions taken to account for potential confounders, these results suggest that exposure to formaldehyde in homes may invoke a subclinical inflammatory response in the airways of healthy children. In their discussion, the author's further suggest that such an inflammatory response may explain some of the observed associations among formaldehyde exposure, respiratory morbidity, and immunologic responses. Their tentative hypothesis was that the reported immune response to formaldehyde exposure could result from damage to the airway epithelium, causing increased airway permeability and other inflammatory changes that would allow easier penetration of inhaled allergens to cells of the immune system. The association between formaldehyde concentrations and exhaled nitric oxide levels in this study occurred in children with no previous airway damage and was independent of atopy.

B. Summary of Key Animal Studies

No animal studies are available comparing effects of formaldehyde exposure early in life versus later in life. However, data from animal studies indicate that formaldehyde exposure may exacerbate asthma. OEHHA considers asthma to impact children more than adults and thus substances that either exacerbate or induce asthma should be considered for listing under SB 25 (see also Section II of the Introduction.) Animal studies bearing on the issue of induction and exacerbation of asthma are summarized here.

Amdur (1960) exposed groups of 4 to 18 guinea pigs to 0.05, 0.31, 0.58, 1.22, 3.6, 11.0, or 49 ppm formaldehyde for one hour. At the end of exposure and one hour later, the investigator measured intrapleural pressure, tidal volume, and rate of flow to the lungs, and calculated resistance to flow and lung compliance. Resistance and compliance were significantly different from the control level for the 0.31 ppm exposure ($p<0.05$) and increasingly significant at higher concentrations. One hour later only the 49 ppm exposure remained significant ($p<0.01$). Amdur (1960) also cannulated the tracheas of groups of 6 to 10 guinea pigs and exposed them for one hour to 0.90, 5.2, 20, or 50 ppm formaldehyde, and 1.14 or 3.6 ppm formaldehyde with 10 mg/m³ sodium chloride. With the protective effect of the trachea bypassed, the resistance and compliance changed substantially and the addition of sodium chloride further enhanced the effect, including a significant effect after one hour for the 1.14 ppm formaldehyde exposure. These results show that formaldehyde that reaches the lungs has a marked effect on airways resistance and compliance, in addition to an effect on the upper airways.

Swiecechowski *et al.* (1993) exposed groups of five to seven guinea pigs to 0.86, 3.4, 9.4, or 31.1 ppm (1.1, 4.2, 11.6, or 38.6 mg/m³) formaldehyde for 2 hours, or to 0.11, 0.31, 0.59, or 1.05 ppm (0.14, 0.38, 0.73, 1.30 mg/m³) formaldehyde for 8 hours. An 8-hour exposure to ≥ 0.3 ppm (≥ 0.4 mg/m³) formaldehyde was sufficient to produce a significant increase in airway reactivity. Similar effects occurred after > 9 ppm (> 11 mg/m³) formaldehyde for the 2-hour exposure group. Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine (or carbachol) *ex vivo*. No inflammation or epithelial damage was seen up to 4 days post exposure.

The researchers suggest that duration of exposure is important to the induction of airway hyperreactivity from formaldehyde, and that prolonged (8-hour), low-level exposures may generate abnormal physiologic responses in the airways not detectable after acute (2-hour) exposures.

Riedel *et al.* (1996) studied the influence of formaldehyde exposure on allergic sensitization in the guinea pig. They exposed three groups of guinea pigs (12/group), to clean air or two different formaldehyde concentrations (0.13 and 0.25 ppm) over 5 consecutive days. Following exposure they sensitized the animals with allergen by inhalation of 0.5% ovalbumin (OA). Three weeks later, they performed specific bronchial provocation with OA using a body plethysmographic measurement of compressed air. Also they determined specific anti-OA-IgG1 antibodies in serum. In another group of six animals, they examined the respiratory tract histologically for signs of inflammation directly after the end of formaldehyde or clean air exposure. In the group exposed to 0.25 ppm formaldehyde, 10/12 animals were found to be sensitized to OA (positive reaction on specific provocation) vs. 3/12 animals in the control group ($P < 0.01$). Furthermore, compressed air measurements of specific bronchial provocation and serum anti-OA-antibodies were significantly higher in the 0.25 ppm formaldehyde group than in controls. The median compressed air measurement was 0.35 ml for the formaldehyde-exposed group vs. 0.09 ml for the controls ($p < 0.01$), indicating increased bronchial obstruction. The median anti-OA-IgG1 measured in the formaldehyde-exposed group was 13 vs. less than 10 EU in the controls ($p < 0.05$), indicating enhanced sensitization. In the group exposed to 0.13 ppm formaldehyde, no significant difference was found compared to the control group. Histological examination found edema of the bronchial mucosa, but there was no sign of inflammation of the lower airways in formaldehyde-exposed guinea pigs. The investigators concluded that short-term exposure to a low concentration of formaldehyde (0.25 ppm) can significantly enhance sensitization to inhaled allergens in the guinea pig.

V. Additional Information

A. Respiratory Effects in Adults

Numerous controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritative and pulmonary effects in adults. These studies are discussed in detail in OEHHA (1999 and 2000). While the limited data available in children indicate adverse health effects of formaldehyde at concentrations as low as 30 ppb, the most sensitive studies in adults indicate health impacts at higher concentrations.

In a recent review of the medical and toxicological literature, OEHHA (2000) found a NOAEL and LOAEL of $32 \mu\text{g}/\text{m}^3$ (26 ppb) and $92 \mu\text{g}/\text{m}^3$ (75 ppb), respectively, after adjustment for exposure continuity. These were based on nasal and eye irritation, nasal obstruction, and lower airway discomfort, as well as histological nasal lesions (including rhinitis, squamous metaplasia and dysplasia) in chemical plant workers (Wilhelmsson and Holstrom, 1992; Edling *et al.*, 1988). Formaldehyde concentrations of 0.2–2 ppm in a variety of workplace settings have been associated with significant decreases in lung function (measurements include FVC, FEV₁, FEV₁/FVC, FEF₂₅₋₇₅ and FEF₇₅₋₈₅), respiratory irritation, eye and nose discomfort, deep airway discomfort, diminished olfactory ability, and

delayed mucociliary clearance (Alexandersson and Hedenstierna, 1989; Kilburn *et al.*, 1989; Malaka and Kodama, 1990; Holmstrom and Wilhelmsson, 1988). Alexandersson *et al.* (1982) reported eye and throat irritation as well as significant reductions in lung function in workers exposed to a mean formaldehyde concentration of 0.36 ppm (range = 0.04 - 1.25 ppm). Symptoms reported in residential setting include concentration-related eye, nose and throat irritation and headaches in persons living in mobile homes (concentrations greater than 0.1 ppm; Ritchie and Lehen, 1987) or homes insulated with urea-formaldehyde foam (at 0.043 ppm; Border *et al.*, 1988), and exacerbation of chronic respiratory and allergy problems (0.09 ppm; Liu *et al.*, 1991).

B. Formaldehyde, Asthma, and Adults

It is unclear from the literature whether or not formaldehyde can induce or exacerbate asthma in adults. It appears that the effects of formaldehyde on asthmatics may be dependent on previous, repeated exposure to formaldehyde. Burge *et al.* (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors (1.5 to 20.6 ppm for brief durations) exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV₁) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m³) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard *et al.* (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume. Other studies of asthmatics and previously exposed workers did not find statistically significant effects on lung function measurements from challenges of formaldehyde exposure in the range of 0.4 to 3 ppm for up to four hours (ATSDR, 1999). The National Academy of Sciences' Institute of Medicine notes in their report "Clearing the Air. Asthma and Indoor Air Exposures" (NAS, 2000), that there is suggestive evidence of formaldehyde exposure and wheezing or respiratory symptoms but insufficient evidence to determine whether or not an association exists between formaldehyde exposure and asthma development.

These studies demonstrate a wide range of asthmatic responses, suggesting that formaldehyde may have an important effect in some adults but not others. In addition to different cellular responses, the uptake in the mucous lining of the airways may also differ among the study populations. Another factor in some of these results is different durations of exposure. The results of Swiecechowski *et al.* (1993) in guinea pigs suggests that the longer exposures at lower concentrations of formaldehyde may amplify the effect to be the same as shorter exposures at higher concentrations. Although there are no comparable studies for children, their immature immune systems are likely to produce responses that are more varied as well as shifted toward sensitization to formaldehyde exposure.

While these studies have not been convincing that formaldehyde exposure exacerbates asthma in adults, the studies in adults may not be applicable to children to allergic asthma in children. As previously noted, Krzyzanowski *et al.* (1990) found that asthmatic children were more affected by formaldehyde than non-asthmatic children. In addition, allergic sensitization, as measured by elevated levels of

formaldehyde-specific IgE, has been noted in two studies of children exposed to environmental levels of formaldehyde (Wantke *et al.*, 1996; Garrett *et al.*, 1999). The allergic sensitization may make children more sensitive to development of serious conditions such as asthma, although this has not been studied for formaldehyde. In addition to the data in children, animal data provide support for the contention that formaldehyde exposure may exacerbate asthma. Amdur (1960) showed that formaldehyde has a marked effect on airway resistance and compliance in guinea pigs. More importantly, Swieczkowski *et al.* (1993) showed that duration of exposure is important to the induction of airway hyperreactivity from formaldehyde. In this latter study, an 8-hour exposure to 1 ppm formaldehyde produced greater than expected effects on airway constriction compared to a 2-hour exposure at higher concentrations, suggesting that prolonged, low-level formaldehyde exposures may generate abnormal physiologic responses in the airways not detectable after acute exposures.

C. Regulatory Background

The California Environmental Protection Agency (Cal/EPA) in 1992 identified formaldehyde as a Toxic Air Contaminant. OEHHA's health effects assessment focused primarily on carcinogenicity and the development of the cancer potency factor of $5.0 \times 10^{-6} (\mu\text{g}/\text{m}^3)^{-1}$ ($7 \times 10^{-6} \text{ ppb}^{-1}$) for a 70 year lifetime. This value was based primarily on nasal cancers in rats, using a metabolic model. The International Agency for Research on Cancer (IARC) in 1987 and again in 1995 found the evidence of carcinogenicity of formaldehyde to be limited in humans and sufficient in animals, and classified formaldehyde as a probable human carcinogen, Category 2A (IARC, 1995). The U.S. Environmental Protection Agency (U.S. EPA) in 1987 classified formaldehyde in Group B-1, a probable human carcinogen, and determined a cancer potency factor of $6.5 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$, based on nasal cancers in rats. This value was modified in 1991 to $1.3 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$ for the Integrated Risk Information System (IRIS). The Occupational Safety and Health Administration (OSHA) in 1987 concluded that formaldehyde should be regarded as an occupational carcinogen.

The chronic reference exposure level (REL) for formaldehyde is $3 \mu\text{g}/\text{m}^3$ (2 ppb) (OEHHA, 2000). This value was based on a NOAEL of $32 \mu\text{g}/\text{m}^3$ (26 ppb) for symptoms of irritation in workers. The acute REL for formaldehyde is 74 ppb based on irritation of asthmatics. The World Health Organization (WHO) in 1989 determined a threshold value of $60 \mu\text{g}/\text{m}^3$ (50 ppb). The National Institute of Occupational Safety and Health (NIOSH, 1992) in 1988 determined a REL-TWA (Time-Weighted Average) of $20 \mu\text{g}/\text{m}^3$ (16 ppb), based on the threshold of reliable measurement at that time. The Occupational Safety and Health Administration (OSHA) in 1992 established a PEL-TWA (Permissible Exposure Level) of $920 \mu\text{g}/\text{m}^3$ (750 ppb), based on reducing risk due to cancer and eye, nose and throat irritation and sensitization. The American Conference of Governmental Industrial Hygienists (ACGIH) assigned a Threshold Limit Value (TLV) of $360 \mu\text{g}/\text{m}^3$ (300 ppb), based on irritation in less sensitive workers but not protecting the most sensitive workers. The Agency for Toxic Substances and Disease Registry (ATSDR) in 1999 derived a chronic Minimal Risk Level (MRL) of $10 \mu\text{g}/\text{m}^3$ (8 ppb) based on a study of changes in nasal tissue in workers.

VI. Conclusions

Formaldehyde is a respiratory irritant. Formaldehyde exposure is associated with decrements in lung function and elevated respiratory symptoms in children. One study that evaluated both children and adults found that children appear to be more sensitive than adults (Krzyzanowski et al., 1990) although the effect was seen primarily in children also exposed to ETS. There is extensive exposure to formaldehyde particularly indoors. Although there is some evidence indicating children may be more sensitive to formaldehyde respiratory toxicity, at this time, OEHHA has placed formaldehyde in Tier 2. OEHHA may revisit listing formaldehyde in the future, particularly if more information becomes available regarding differential toxicity between children and adults.

VII. References

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